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Research Article

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Practical Synthesis of Pyrido [1,2-A] Benzimidazoles Via Multicomponent Reactions

Çok Bileşenli Tepkimeler Yoluyla Pirido [1,2-A] Benzimidazollarin Pratik Sentezi

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ABSTRACT

A facile and efficient synthesis of 1-amino-3-(4-substituted)-4-nitro-3,5-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-2-carbonitriles was conducted via one-pot multicomponent reaction of 2-(nitromethylene)-2,3-dihydro-1H-benzo[d]imidazole withmalononitrile and aromatic aldehydes. Besides, no tedious work-up procedure was necessary for the isolation of desired products which were precipitated out of reaction medium in pure state. Ten new title compounds were characterized by the means of physical and spectroscopic methods (m.p., IR, NMR and TOF-MS analyses).

Key Words

Heterocyclic ketene aminal, enamine, multicomponent, benzimidazole, pyrido[1,2-a]benzimidazole.

ÖZ

Tek basamakta siklik enamin (2-(nitrometilen)-2,3-dihidro-1H-benzo[d]imidazol), malononitril ve aromatik aldehit ile çoklu bileşenli tepkime üzerinden 1-amino-3-(4-substitue)-4-nitro-3,5-dihidrobenzo[4,5]imidazo[1,2-a]piridin-2-karbonitril lerin kolay ve etkili bir biçimde sentezi açığa çıkarıldı. Ayrıca, istenilen ürünlerin eldesinde herhangi bir saflaştırma prosedürü gerektirmedi. Bütün ürünler saf olarak tepkime ortamında çökeltildi. On yeni yapı fiziksel ve spektroskopik yöntemler kullanılarak karakterize edildi (e.n., IR, NMR ve TOF-MS analizleri).

Anahtar Kelimeler

Heterosiklik keten aminal, enamin, çok-bileşenli, benzimidazol, pirido[1,2-a]benzimidazol.

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INTRODUCTION

Benzimidazole as an important heterocycle represents key structure of many biologically active compounds [1]. Molecules containing this core have taken great attention in the field of medicinal chemistry during last decades. Especially, the pyrido[1,2-a]benzimidazoles exhibited various bioactivities such as anticancer [2], antimalarial [3], antiproliferative [4], antifungal [5], antiviral and antipyretic agents [3]. Moreover, this heterocylic unit can also be found as embedded in a commercially available antibiotic drug, Rifaximin [6] (Figure 1).

Due to aformentioned biological properties and medicinal applications, development of efficient and atom economic strategies through the synthesis of pyrido[1,2-a] benzimidazoles has attracted considerable interest [7]. Up to now, many methods have been utilized for the synthesis of these heterocycles by transition metal-catalyzed nucleophilic substitution of 2-aminopyridines with o-dihaloarenes (1) [8], C-N coupling of 2-haloanilines with 2-halopyridines, intramolecular cyclization of N-aryl-2-aminopyridines (2) [9], metal-free annulation of arenes with 2-aminopyridine derivatives (3) [10] and cyclocondensation of benzimidazoles with bifunctional reagents (4) (Figure 2) [11].

Although the synthetic methods in recent literature are convenient for the construction of pyrido[1,2-a]benzimidazoles, many of them may require expensive transition-metal catalysts, elevated reaction temperatures, extensive reaction times and tedious work-up procedures [7]. The difficulties in the preparation of this heterocycles prompted us to investigate simple and work-up free synthetic methodology. In this context, we herein report one-pot synthetic method by the multicomponent reaction of 2-(nitromethylene)-2,3-dihydro-1H-benzo[d]imidazoles with an active methylene compound, malononitrile, and aromatic aldehydes in a single-step without further purification.

MATERIALS and METHODS

General

Infrared spectra were recorded on a SHIMADZU FTIR-8400S instrument using KBr pellets. HRMS were run on a Waters Lct Premier XE oa-TOF Mass Spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL-ECS400 Delta2 NMR spectrometer (400 MHz for proton and 100 MHz for carbon) at ambient temperature. All chemical shifts were reported in ppm downfield from TMS. Coupling constants (J) are reported in Hz. Melting points were determined on a MELTEMP apparatus and uncorrected. TLC was performed using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate were used for visualization of the TLC spots. Cyclic enamines, (2-(nitromethylene)-2,3-dihydro-1H-benzo[d]imidazole and ((E)-5-methyl-2-

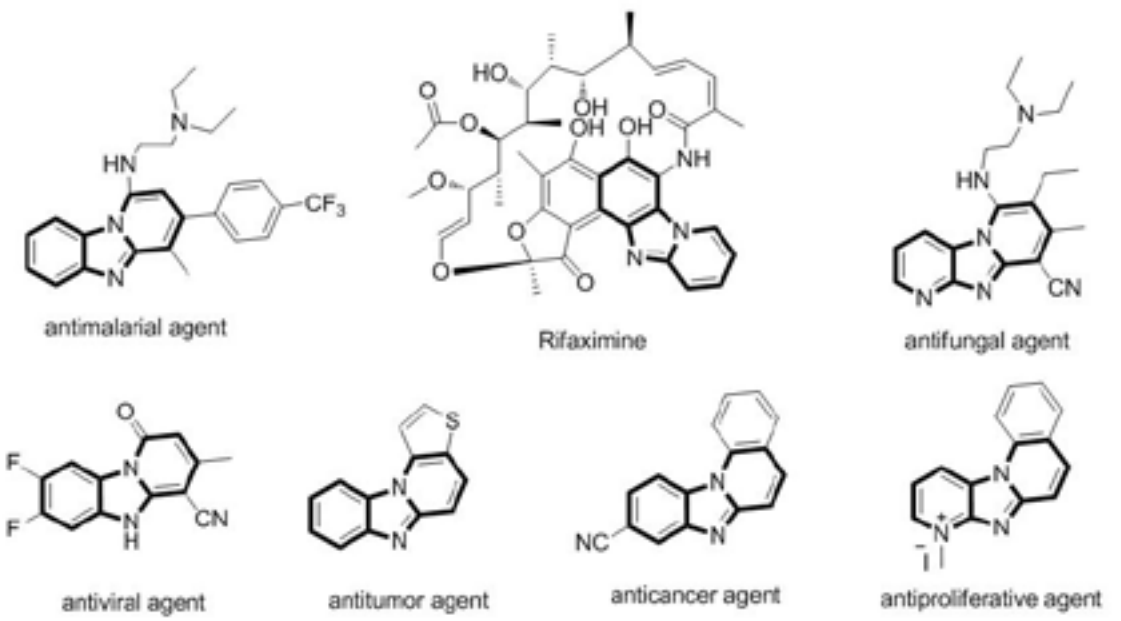


Figure 1. Some biologically important pyrido[1,2-a]benzimidazole derivatives.

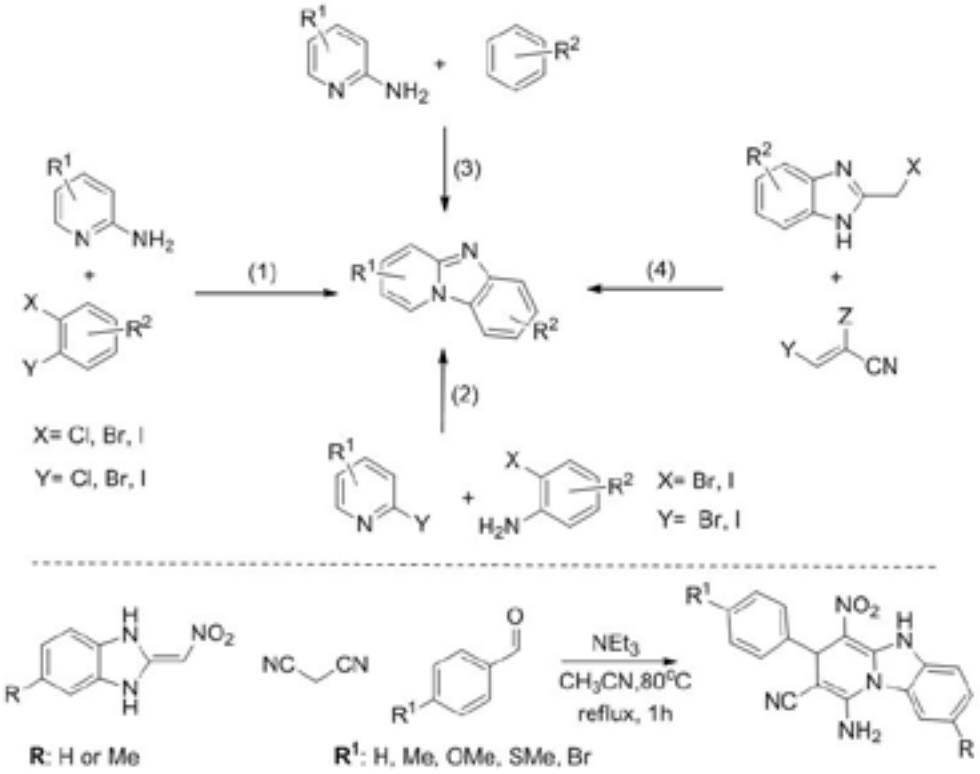


Figure 2. Methods for the synthesis of pyrido[1,2-a]benzimidazoles.

(nitromethylene)-2,3-dihydro-1H-benzo[d]imidazole)), were prepared according to the literature method [12].

General Procedure for the Preparation of Pompound 4a-l

Aromatic aldehyde (1 mmol), heterocyclic enamines (1 mmol) and malononitrile (1 mmol) were mixed in acetonitrile (15 mL) in a round-bottomed flask, and the reaction mixture was stirred at 60°C for 15 min. Triethylamine (0.5 mmol) was added and the reaction mixture was heated under reflux for 1 h (Table 1). After completion of the reaction, the precipitated solid was filtered, and washed with Et_2O (25 mL) to give the pure products with data given below.

1-amino-4-nitro-3-phenyl-3,5-dihydrobenzo[4,5] imidazo[1,2-a]pyridine-2-carbonitrile (4a): Yellow solid. Yield: 78% m.p. 245°C (decomp.). IR (KBr): ν = 3456 (NH_2), 2202 (CN), 1670, 1624, 1477, 1388, 1300, 1091, 1049, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 12.96 (s, 1H, NH), 7.89 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.45 – 7.21 (m, 4H), 7.18 (d, J = 7.1 Hz, 3H), 6.46 (s, 2H, NH_2), 4.95 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 148.21, 144.73, 143.49, 132.48, 129.05, 128.60, 127.55, 127.29, 125.60, 124.25, 119.51, 115.21, 113.45, 70.20, 41.59, 31.11; HRMS (-ESI-TOF) calcd for $C_{18}H_{13}N_5O_2$ $[M-H]^-$ 331.1069, found 331.1066.

1-amino-4-nitro-3-(p-tolyl)-3,5-dihydrobenzo[4,5] imidazo[1,2-a]pyridine-2-carbonitrile (4b): Yellow solid. Yield: 82% m.p. 245°C (decomp.). IR (KBr): ν = 3462, 3416 (NH_2), 2200 (CN), 1670, 1622, 1479, 1398, 1301, 1089, 1045, 734 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 13.11 (s, 1H, NH), 7.87 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.5 Hz, 2H), 7.38 – 7.23 (m, 4H), 6.55 (s, 2H, NH_2), 4.87 (s, 1H), 2.19 (s, 3H, CH_3) ;^{13}C NMR (101 MHz, DMSO) δ 148.12, 144.57, 140.53, 136.75, 132.40, 129.60, 128.56, 127.23, 125.61, 124.29, 119.65, 115.31, 113.42, 105.71, 70.16, 41.15, 21.13; HRMS (-ESI-TOF) calcd for $C_{19}H_{15}N_5O_2$ $[M-H]^-$ 345.1226, found 345.1209.

1-amino-3-(4-methoxyphenyl)-4-nitro-3,5-dihydrobenzo [4,5]imidazo[1,2-a]pyridine-2-carbonitrile (4c): Yellow solid. Yield: 85% m.p. 242°C (decomp.). IR (KBr): ν = 3448, 3244 (NH_2), 2200 (CN), 1670, 1618, 1514, 1394, 1301, 1093, 1045, 736 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 13.13 (s, 1H, NH), 7.88 (d, J = 8.1 Hz, 1H), 7.57 (d, J =

7.6 Hz, 1H), 7.39 – 7.23 (m, 2H), 7.08 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 6.9 Hz, 2H), 6.55 (s, 2H, NH_2), 4.86 (s, 1H), 3.65 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, DMSO) δ 158.85, 148.07, 144.48, 135.57, 132.40, 128.57, 128.47, 125.61, 124.27, 119.69, 115.31, 114.41, 113.41, 105.91, 70.31, 55.57, 40.74; HRMS (-ESI-TOF) calcd for $C_{19}H_{15}N_5O_3$ [M-H]$^-$ 360.1097, found 360.1141.

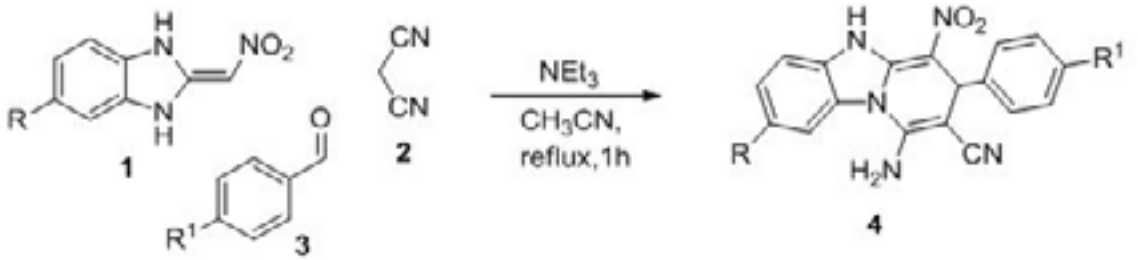
1-amino-3-(4-(methylthio)phenyl)-4-nitro-3,5-dihydrobenzo [4,5]imidazo[1,2-a]pyridine-2-carbonitrile (4d): Yellow solid. Yield: 80% m.p. 247°C (decomp.). IR (KBr): ν = 3458, 3246 (NH_2), 2200 (CN), 1670, 1620, 1477, 1394, 1301, 1091, 1045, 736 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 13.00 (s, 1H, NH), 7.89 (d, J = 6.5 Hz, 1H), 7.58 (d, J = 5.5 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.22 – 7.05 (m, 3H), 6.46 (s, 2H, NH_2), 4.91 (s, 1H), 2.38 (s, 3H, SCH_3) ;^{13}C NMR (101 MHz, DMSO) δ 148.21, 144.64, 140.33, 137.25, 132.46, 128.60, 127.99, 127.02, 125.60, 124.26, 119.47, 115.20, 113.45, 105.59, 70.09, 41.13, 15.52; HRMS (-ESI-TOF) calcd for $C_{19}H_{15}N_5O_2S$ [M-H]$^-$ 376.0868, found 376.0871.

1-amino-3-(4-bromophenyl)-4-nitro-3,5-dihydrobenzo[4,5] imidazo[1,2-a]pyridine-2-carbonitrile (4e): Yellow solid. Yield: 87% m.p. 247°C (decomp.). IR (KBr): ν = 3460, 3248 (NH_2), 2198(CN), 1670, 1620, 1477, 1394, 1300, 1091, 1045, 736 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 13.13 (s, 1H, NH), 7.88 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 5.5 Hz, 2H), 7.38 – 7.07 (m, 4H), 6.50 (s, 2H, NH_2), 4.94 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 148.33, 144.53, 142.87, 132.43, 131.90, 129.77, 128.57, 125.63, 124.31, 120.61, 119.49, 115.31, 113.46, 105.33, 69.37, 41.23; HRMS (-ESI-TOF) calcd for $C_{18}H_{12}BrN_5O_2$ [M-H]$^-$ 408.0096, found 408.0098.

1-amino-8-methyl-4-nitro-3-phenyl-3,5-dihydrobenzo[4,5] imidazo[1,2-a]pyridine-2-carbonitrile (4f): Yellow solid. Yield: 75% m.p. 246°C (decomp.). IR (KBr): ν = 3397, 3253 (NH_2), 2191 (CN), 1657, 1629, 1433, 1365, 1284, 1093, 1040, 708 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 12.92 (s, 1H, NH), 7.74 (d, J = 7.3 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 7.0 Hz, 2H), 7.16 (d, J = 7.8 Hz, 4H), 6.48 (s, 2H, NH_2), 4.93 (s, 1H), 2.39 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO) δ 148.24, 144.68, 143.53, 135.44, 133.98, 129.04, 127.53, 127.25, 126.45, 125.15, 119.62, 115.38, 113.09, 105.54, 69.76, 41.53, 21.76; HRMS (-ESI-TOF) calcd for $C_{19}H_{15}N_5O_2$ [M-H]$^-$ 344.1147, found 344.1140.

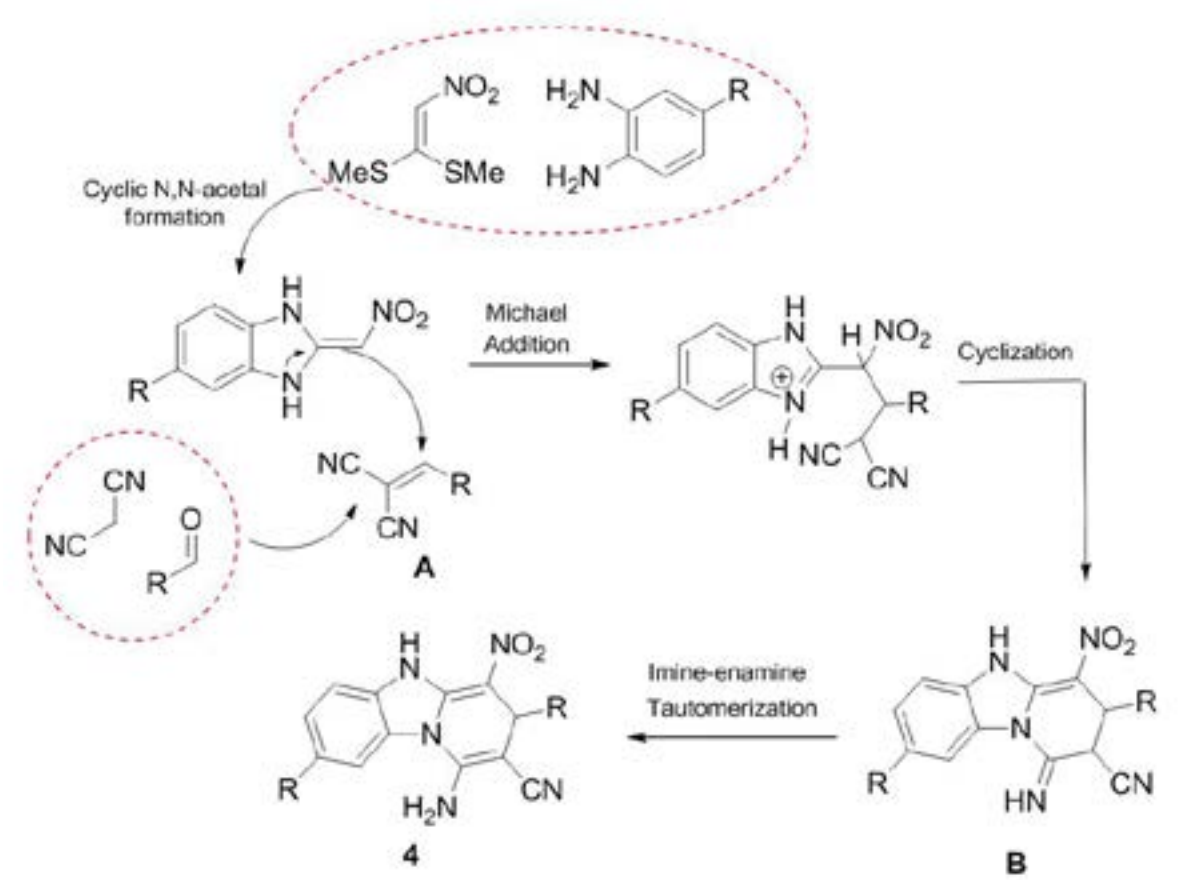
1-amino-8-methyl-4-nitro-3-(p-tolyl)-3,5-dihydrobenzo[4,5] imidazo[1,2-a]pyridine-2-carbonitrile (4g): Yellow solid. Yield: 84% m.p. 244°C (decomp.). IR (KBr): ν = 3408, 3302 (NH_2), 2202 (CN), 1670, 1624, 1458, 1396,

Table 1. Reactions of 2-(nitromethylene)-2,3-dihydro-1H-benzo[d]imidazoles with malononitrile and aromatic aldehydes.



Entry	Compound	R	R^1	Yield(%)[a]
1	4a	H	H	78
2	4b	H	Me	82
3	4c	H	OMe	85
4	4d	H	SMe	80
5	4e	H	Br	87
6	4f	Me	H	75
7	4g	Me	Me	84
8	4h	Me	OMe	82
9	4i	Me	SMe	78
10	4l	Me	Br	85

a Yields after purification.



Scheme 1. Possible reaction mechanism for formation of compound 4.

1282, 1093, 1043, 788 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 12.92 (s, 1H, NH), 7.75 (d, J = 8.5 Hz, 1H), 7.38 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.04 (s, 4H), 6.41 (s, 2H, NH_2), 4.89 (s, 1H), 2.37 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO) δ 148.06, 144.64, 140.59, 136.71, 135.42, 132.63, 129.57, 127.15, 126.59, 125.13, 119.58, 114.79, 113.41, 105.65, 70.04, 41.17, 21.45, 21.08; HRMS (-ESI-TOF) calcd for $C_{20}H_{17}N_5O_2$ $[M-H]^-$ 358.1304, found 358.1328.

1-amino-3-(4-methoxyphenyl)-8-methyl-4-nitro-3,5-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-2-carbonitrile (4h): Yellow solid. Yield: 82% m.p. 240°C (decomp.). IR (KBr): v = 3456, 3253 (NH_2), 2199 (CN), 1670, 1622, 1458, 1396, 1282, 1093, 1043, 788 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 12.88 (s, 1H, NH), 7.75 (d, J = 8.5 Hz, 1H), 7.37 (s, 1H), 7.08 (t, J = 8.3 Hz, 3H), 6.79 (d, J = 8.5 Hz, 2H), 6.40 (s, 2H, NH_2), 4.88 (s, 1H), 3.66 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO) δ 158.93, 148.02, 144.60, 135.68, 135.38, 132.75, 128.38, 126.62, 125.09, 119.62, 114.79, 114.50, 113.43, 105.83, 70.15, 55.63, 40.81, 21.45; HRMS (-ESI-TOF) calcd for $C_{20}H_{17}N_5O_3$ $[M-H]^-$ 374.1253, found 374.1286.

1-amino-8-methyl-3-(4-(methylthio)phenyl)-4-nitro-3,5-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-2-carbonitrile (4i): Yellow solid. Yield: 78% m.p. 246°C (decomp.). IR (KBr): v = 3456, 3298 (NH_2), 2200 (CN), 1670, 1622, 1456, 1392, 1284, 1095, 1043, 788 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 12.92 (s, 1H, NH), 7.75 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 6.1 Hz, 4H), 6.46 (s, 2H, NH_2), 4.90 (s, 1H), 2.38 (s, 3H, SCH_3), 2.37 (s, 3H, CH_3) ;^{13}C NMR (101 MHz, DMSO) δ 148.16, 144.62, 140.39, 137.22, 135.43, 132.69, 127.94, 127.02, 126.60, 125.14, 119.53, 114.79, 113.44, 105.51, 69.69, 41.12, 21.45, 15.53; HRMS (-ESI-TOF) calcd for $C_{20}H_{17}N_5O_2S$ $[M-H]^-$ 390.1025, found 390.1001

1-amino-3-(4-bromophenyl)-8-methyl-4-nitro-3,5-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-2-carbonitrile (4l): Yellow solid. Yield: 85% m.p. 247°C (decomp.). IR (KBr): v = 3460, 3278 (NH_2), 2200 (CN), 1670, 1624, 1456, 1394, 1249, 1095, 1043, 788 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 12.96 (s, 1H, NH), 7.76 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 7.7 Hz, 3H), 7.15 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 8.1 Hz, 1H), 6.50 (s, 2H, NH_2), 4.93 (s, 1H), 2.37 (s, 3H, CH_3);

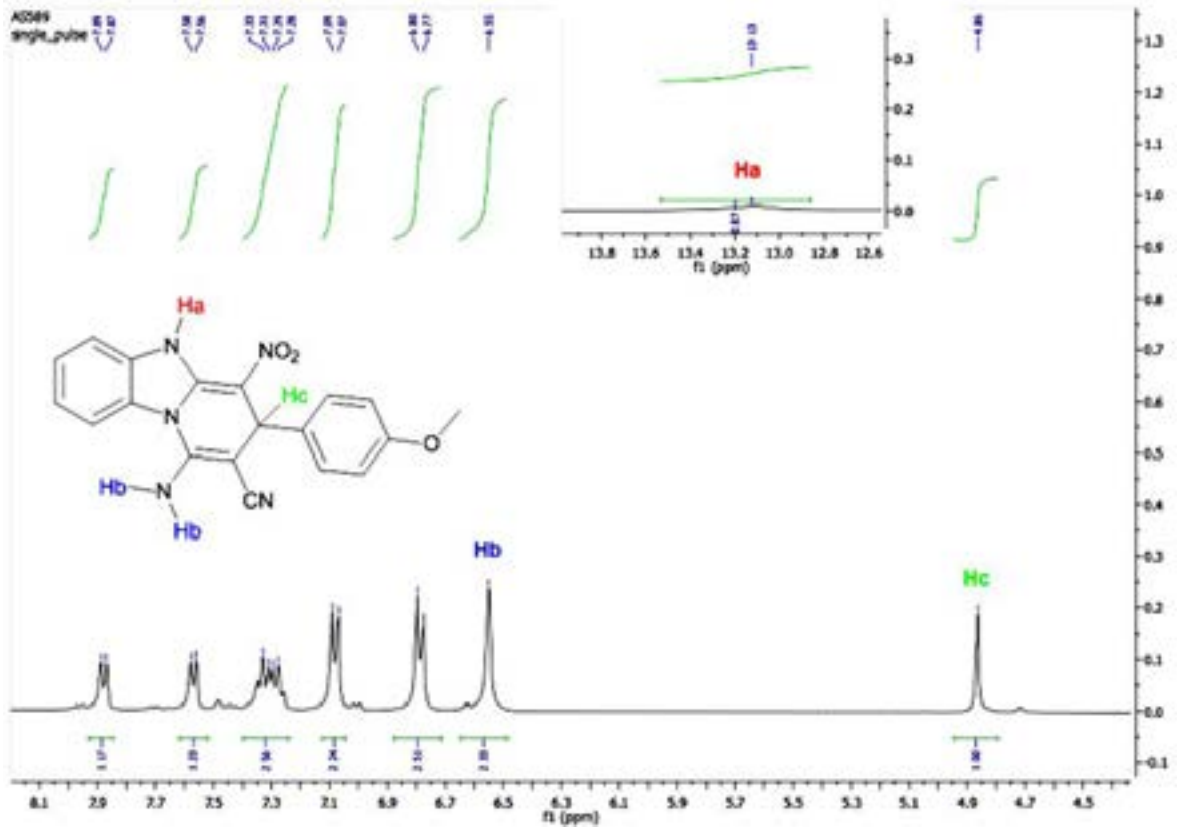


Figure 3. Expanded ^{1}H NMR spectrum of compound 4c.

^{13}C NMR (101 MHz, DMSO) δ 148.27, 144.58, 142.92, 135.47, 132.64, 131.89, 129.67, 126.59, 125.18, 120.58, 119.41, 114.80, 113.45, 105.25, 69.24, 41.26, 21.45; HRMS (-ESI-TOF) calcd for $C_{19}H_{14}BrN_5O_2$ [M-H]$^-$ 422.0225, found 422.0253.

RESULTS and DISCUSSION

Heterocyclic ketene enaminals (HKAs) have been widely used as valuable intermediates in multicomponent reactions due to their bisnucleophilic property that allow reaction with various substrates such as unsaturated carbonyl compounds [13], iminium ions [14], diazonium salts [12] and olefins bearing electron-withdrawing group (CN, SO_2Ph, CO_2Ph) [15].

Our initial efforts to synthesize cyclic enamine containing benzimidazole scaffold that was derived from the condensation reaction between substituted o-phenylenediamine and 1,1-bis(methylthio)-2-nitroethylene, and characterized by IR, ^{1}H NMR and physical data such as melting point. To the best of our knowledge, there has been only one example mentioned in literature regarding multicomponent reaction of o-phenylenediamine, 1,1-bis(methylthio)-2-nitroethylene, malononitrile and salicyaldehyde [16]. However, no other aromatic aldehydes were used for this reaction.

Therefore, after preparation of cyclic enamines, we decided to perform multicomponent reaction by introducing related cyclic enamines 1 with malononitrile 2 and aromatic aldehydes 3 in CH_3CN at reflux temperature. After 1 hour, consumption of cyclic enamine was controlled by TLC to understand the completion of reaction. The reaction afforded the desired pyrido[1,2-a]benzimidazoles 4 in high yield (75-87%) without any purification step. The reaction condition and scope of reaction (in Table 1) clearly indicates that the reaction proceeded efficiently and smoothly with a variety of aromatic aldehydes.

The plausible reaction mechanism was proposed for the formation of corresponding pyrido[1,2-a]benzimidazoles. Presumably, the reaction begins by the addition of cyclic enamines 3 to in situ formed arylidinemalononitrile (A) which was early derived from the Knoevenagel condensation of the aldehyde 3 with malononitrile 2, and then sec-

ondary amine group of enamine attacks to nitrile carbon and cyclization affords intermediate B. This is followed by imine-enamine tautomerization of B to give desired product 4.

The structures of pyrido[1,2-a]benzimidazoles 4a-l were identified by means of IR, NMR and HRMS data. In IR spectra for compounds 4a-l, most indicative vibrational bands of NH, NH_2 and CN group appeared at around 3420, 3314-3250 and 2200 cm^{-1}, respectively. In the ^{1}H- and ^{13}C-NMR spectra of products 4a-l, the most confirmative proton signal was the methinic CH (Hc) of the formed dihydropyrimidine ring and it reasonated as singlet in a range of 4.86-4.95 ppm. Whereas another confirmative proton NMR signals belonging to NH_2 (Hb) resonated at ca. 6.40-6.55 ppm. The NH (Ha) proton of benzimidazole ring resonated at around 12.90 ppm as broad singlet and in some cases they were not easily detected (Figure 3). As for ^{13}CNMR shifts of the compound 4a-l, the resonance of the only one aliphatic carbon attached to substituted phenyl ring appeared at around 41 ppm, and the double bond carbon bearing CN group did at around 67 ppm. This indicative carbon signals are in accord with previous report where only o-hydroxyphenyl substituted of compound 4 has been exploited [16]. Also, HRMS measurements revealed that M-H values accurately coincide with the molecular formulas of the proposed structures.

Conclusion

In summary, we described a facile and efficient method for the construction of new pyrido[1,2-a]benzimidazoles via multicomponent reaction of heterocyclic enamines (1) without using tedious purification steps and identified the pyrido[1,2-a]benzimidazoles products (4) by means of spectroscopic methods successfully.

Acknowledgments

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